Age-Specific Genetic Effects for Blood Pressure

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Correlations between relatives were determined for systolic and diastolic blood pressure. The correlations decrease as age differences between relatives increase in a Norwegian sample with 43 751 parent-offspring pairs, 19 140 pairs of siblings, and 169 pairs of twins. A simple biometric model specifying only age-specific genetic additive effects and environmental effects fitted well to correlations between cotwins, pairs of siblings, and parent-offspring dyads in subsets of relatives grouped by age differences. None of the environmental effects appeared to be due to environmental factors that are shared by family members. Models that excluded a parameter for the age-specific genetic influence did not fit the data. The results may partly explain what seems to be a discrepancy between relatively low parent-offspring correlations from previous nuclear family studies and high correlations from twin studies, especially in identical twins. (Hypertension. 1993;22:789-795.)

KEY WORDS • blood pressure • hypertension, genetic • age factors • families • genetics • genes

Individual variation in blood pressure is to some extent determined by genes, but its genetic architecture is not well known. Genetic variance is typically divided into additive variance and variance caused by genetic dominance. Whereas both alleles of an additively acting gene contribute equally to the trait influenced by this gene, one of the two alleles of a dominant/recessive gene is dominant over the other. For instance, two "blue" alleles give blue eyes, two "brown" alleles give brown eyes, and one of each give brown eyes rather than something in between because brown is dominant and blue is recessive. It is not clear whether or to what extent blood pressure is affected by genetic dominance. In general, twin studies do not permit a separation of the effects of genetic dominance from genetic additive effects. In the presence of dominance, broad heritability estimates, which include the joint effects of dominant/recessive genes and genetic additive effects, are somewhat inflated in twin studies. In other words, the fact that such estimates reported from twin studies1-9 are higher than those reported from nuclear family9-19 and adoption studies10-22 may suggest the existence of genetic dominance. Higher correlations in siblings than in parent-offspring pairs9,11,15,18,23 are in agreement with the dominance hypothesis because the siblings, unlike parents and offspring, share some of the effects of genetic dominance. However, the higher correlation in siblings may also reflect environmental factors shared by siblings (environmental sibling effects) but not shared by parents and their offspring.

Alternatively, a pattern of relatively high correlations in twins, moderate correlations in siblings, and low correlations in parents and offspring may reflect age-specific effects of genes or environmental factors. Several traits, such as male baldness, are affected by genes that start acting at a certain age. It is perhaps harder to find examples of age-specific environmental effects, but cigarette smoking as an environmental factor for cancer, usually starting in the late teens or early twenties, may serve as one. A developmental model in which the effects of specific genes and environmental factors switch on at different ages and are transmitted forward in time through the phenotype is shown in Fig 1 and described in more detail below.

Age-specific genetic or environmental effects can be studied using longitudinal family data whenever available but may also be examined with cross-sectional data from large samples of first-degree relatives of different ages. Unlike follow-up studies, in which varying phenotypic expression of the same individual genotypes is studied repeatedly across age, cross-sectional studies only examine resemblance between relatives as a function of age differences between relatives. Let the "genotypic value" for an individual be defined as the phenotypic value that a certain genotype would express in an "average" environment. Also, let this phenotypic value be adjusted for any age and sex scalar effects, that is, for age and sex mean trends in the population. Absence of age-specific genetic effects implies that the genotypic value at one age is identical to the genotypic value at any other age. In the case of age-specific genetic effects, the genotypic values at two different ages are not identical, only correlated. This correlation decreases as age-specific effects get stronger and as age span increases. The phenotypic correlation between same-aged relatives, such as twins, is the product of $r_G$. 

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the correlation between each of the cotwins' genotypic values \( r_G = 1.0 \) for identical twins, \( r_G = 0.5 \) for fraternal twins), and \( h \), the correlation between the genotypic and phenotypic values. The phenotypic correlation between different aged relatives, such as siblings with ages \( A_1 \) and \( A_2 \), is the product of \( r_G \) (for siblings), \( h \), and \( r_A \), the latter being the correlation between genotypic values at \( A_1 \) and \( A_2 \). In other words, because relatives who are close in age share more of the age-specific genetic effects (\( r_A \) is high) than relatives who are distant in age (\( r_A \) is lower), the phenotypic correlation between relatives decreases as age differences between relatives increase. In our case, to the extent that different genes control blood pressure at different ages, relatives (eg, pairs of siblings) whose ages differ by, for instance, only 1 year will have more similar blood pressures than siblings whose ages differ by 10 or 20 years. This is true even after adjusting for the general blood pressure increase with age in the population. On the other hand, if the same sets of genes influence blood pressure to the same extent throughout life, age difference will not affect similarity between relatives (except for the scalar effect of age).

It has been shown that blood pressure is partly under the control of different genes in children and adults, and some evidence suggests age-specific effects of genes or environmental factors during adulthood. Here, we will examine such effects for systolic blood pressure (SBP) and diastolic blood pressure (DBP) by observing whether familial resemblance decreases with increasing age difference in the largest family sample with blood pressure data ever studied.

Methods

Sample and Measurement

From 1984 to 1986, the National Health Screening Service requested all people older than 19 years living in the county of Nord-Trøndelag, Norway, to participate in a health screening. Of the total adult population of 85,125, 74,994 people participated. Of the 11.9% (10.1% women, 13.7% men) who did not attend the screening, more than one third returned a questionnaire stating their reason for not meeting (working at sea, military service, staying abroad, sickness, etc). The governmental census agency, the Central Bureau of Statistics (CBS), was able to provide information on first-degree family relationships and spouses/cohabiting partners for all but the oldest part of the screening population. The files including blood pressure data were matched with the family identification data at the CBS and stripped of personal identification numbers before being released to our research group. It was possible to identify 79 pairs of identical, or monozygotic (MZ), and 90 pairs of fraternal, or dizygotic (DZ), twins; 19,140 pairs of siblings; 43,751 pairs of parents and offspring; and 23,936 pairs of spouses with valid data for blood pressure. Written informed consent was not judged to be required by the governmental Data Inspectorate, which approved of the present research, because the information provided to the participants before examination was judged sufficient for participation as such to be understood as a consent. The population and ascertainment have been described more thoroughly elsewhere.

Blood pressures were measured twice with a mercury sphygmomanometer by one of 25 trained nurses in separate rooms. Approximately 20% of the respondents, mostly housewives, attended between noon and 4 PM; the remaining measurements were taken between 4 PM and 8 PM. The subjects did not smoke or engage in any physical activity during the last half hour before the measurement. The manometer cuff was placed at the upper right arm with the subject sitting in a chair at least 4 minutes before the first measurement; the period between the first and second measurement was at least 1 minute. SBP was defined as the nearest even value of millimeters of mercury when the first Korotkoff sound appeared (phase I); DBP was defined as the value of millimeters of mercury at the disappearance of Korotkoff sounds (phase V). In a few cases for whom phase V could not be identified, the pressure at phase IV was used. The sample included individuals under treatment for hypertension; 8.9% of the screening participants—6.3% of the men and 11.3% of the women—reported to have been ever treated.

Correlations between the first and second measurements were .960 for SBP and .935 for DBP. The mean values of the first and second measurements were used. Differences between measurers contributed 1.4% and 2.3% to the variances for SBP and DBP, respectively, suggesting no large measurement error. The test-retest correlations for 7418 subjects that participated in a follow-up study were .73 for SBP and .58 for DBP, with time lags ranging from 41 to 70 months.

Statistical Methods

Before analysis, age effects on means and variances were removed by transforming the blood pressure scores to z scores in separate age groups with 5-year intervals separately for each sex. Pearson correlations for SBP and DBP were computed for the twin pairs and every possible pair of siblings and parent-offspring. All
possible pairs of parents and offspring were grouped according to years of age difference (numbers of pairs in parentheses): Less than 20 years (1149), 20 to 21 (2372), 22 to 23 (3693), 24 to 25 (4580), 26 to 27 (5070), 28 to 29 (5224), 30 to 31 (4850), 32 to 33 (4370), 34 to 35 (3650), 36 to 37 (2954), 38 to 39 (2230), 40 to 41 (1598), 42 to 44 (1239), and 45 or more (772). Pairs of siblings had the following distribution by years of age difference: 1 to 2 (4197), 3 to 4 (4822), 5 to 6 (3608), 7 to 8 (2573), 9 to 10 (1660), 11 to 13 (1366), and 14 or more (914).

Fig 1 shows a developmental model in which the effects of specific environmental factors and genes switch on at different ages and are transmitted forward in time through the phenotype. In the beginning, at age 1, the phenotype, $P_1$, is determined by genes, $G_1$, and environmental factors, $E_1$. The parameters $h$ and $e$ denote the strength of the genetic and environmental effects, respectively. These effects are transmitted to the phenotype $P_2$ at age 2, when new sets of genes and environmental factors, $G_2$ and $E_2$, start to contribute to the phenotype. The contribution of successively new age-specific factors continues until age $N$. It can be shown that under this first-order time-series model, the expected correlations between relatives have the form

$$\exp(-A\delta)\tau e^{-A\delta}e$$

where $A$ denotes age difference in years, and $\tau$ and $e$ are the correlations between additive genotypes and environmental values in relatives, respectively, when all age-specific effects are shared (that is, when the age difference, $A$, is zero, equivalent to $e^{-A\delta}=\exp(-A\delta)=1$). The parameters $\delta$ and $\sigma$ express the decay in the correlation with age differences. Unlike a situation in which the people with the “best” genes are likely to have the best environment, the model assumes that there is no correlation between genotype and environment. It further assumes no effects of dominant/recessive genes and that residual variance is caused by individual environmental factors and measurement error.

Previous results from path analysis of the family correlation structure in the Nord-Trøndelag sample, including first- and second-degree relatives, showed little or no environmental transmission from parents to offspring. There was no evidence of sex-specific effects of genetic or environmental factors except for somewhat lower correlations for DBP in unlike-sexed siblings than in like-sexed siblings. These results justify the utilization of a model for transmission of blood pressure in families that leaves out environmental transmission from parents to offspring and sex-specific parameters. Spouse correlations of .077 and .088 for SBP and DBP, respectively, are highly significant in the large sample but too low to have any noticeable effect on the expected genetic and environmental effects. For this reason, random mating was assumed. A path diagram of this model, including parents and two offspring, is shown in Fig 2. In line with conventions, the observed phenotypic values (blood pressure) in each relative are drawn as rectangles, and latent variables are drawn as circles. The basic model specifies transmission from parental genotypes, $G_o$, to the genotype in offspring, $G_o$. That is, all phenotypic family resemblance results from genetic resemblance. Residual variance is caused by measurement error and environmental factors not shared by relatives. It follows from Mendelian rules that the correlation between genotypic values in parents and offspring is $5$. The parameter $h$ denotes the genetic effects or the extent to which the genotype affects the phenotype. The square of this parameter is the proportion of variance determined by the genetic additive effects, “narrow heritability.” The model may be extended to specify effects of genetic dominance, $d$, or effects of environmental factors shared by siblings and twins but not by other relatives, $s$. DZ twins are not assumed to depart from ordinary siblings. A diagram in which the two siblings (or DZ twins) are replaced by MZ twins only departs from Fig 2 by common genes, $G_o$, for the offspring.

The path model shown in Fig 2 may be combined with a model for age-specific genetic effects, which is a simplified version of the model shown in Fig 1, excluding age-specific environmental factors. The expectations for the correlations between relatives from the full model, including the parameter for age specificity, $\delta$, and the parameters $d$, $s$, and $h$, are

$$r_{pp} = \exp(-A\delta)^{h^2}$$

$$r_{pp} = \exp(-A\delta)^{\frac{h^2}{4}+\frac{d^2}{4}+s^2}$$

$$r_{MZ} = h^2+d^2+s^2$$

for parent-offspring, siblings (and DZ twins), and MZ twins, respectively. For the sake of simplicity, no age-specific effects are assumed for genetic dominance or sibling environment.

The structural equation model was tested by a minimization program described elsewhere based on the SAS NLIN package. The extent to which the expectations fit the set of data points (that is, the correlations between various types of pairs of relatives grouped by age difference) is indicated by a $\chi^2$ value. A high value

![Diagram](http://hyper.ahajournals.org/)

**Fig 2.** Diagram shows a model for genetic transmission from parents to offspring. See text for discussion.
by strict likelihood ratio tests. That is, there is a small overestimate the significance levels that would be found giving estimates that are usually close to the maximum likelihood estimates in kinship studies.31-33 The significance levels associated with DWLS tend somewhat to overestimate the significance levels that would be found by strict likelihood ratio tests. That is, there is a small risk of attaching undue precision to individual parameter estimates and of falsely rejecting a true model. This does not apply for the estimation of age-specific effects, however, which basically depends on the decrease of correlations with increased age differences. The fluctuation of such a trend decreases rather than increases—and the precision improves rather than worsens—as a result of lack of independence between groups of relatives classified by age differences.

**Results**

The correlations between relatives for age- and sex-corrected blood pressure in the total sample are shown in Table 1. The sibling correlations are somewhat higher than the parent-offspring correlations \( z=5.81, P<10^{-7} \) and \( z=3.91, P<10^{-4} \) for SBP and DBP, respectively, pooling the parent-offspring correlations. The MZ twin correlations are slightly (but far from significantly) higher than twice the sibling correlation, which is the expected proportion when all family resemblance is due to genetic additive effects.

Table 2 shows the goodness-of-fit for alternate models to the observed correlations in pairs of relatives with various age differences. A model with only age-specific, additive genetic effects (model 3) fitted just as well as models that also include environmental sibling effects (model 1) or genetic dominance (model 2) for both SBP and DBP. The difference in \( \chi^2 \) values and their respective degrees of freedom between two nested models is itself distributed as a \( \chi^2 \) and tests for the significance of the parameter dropped from the model. Exclusion of the age-specific effects (models 4 through 6) substantially reduced the model fits. Model 5, specifying only genetic additive and dominance effects, was not clearly rejected for SBP \((P=0.07)\), but the difference between the fits for model 5 and the corresponding model including age-specific effects, model 2, was highly significant \((\chi^2=13.12, P=0.0003)\).

Model 3, with only age-specific additive genetic effects (except for individual environmental factors and measurement error), is the best-fitting model. The estimates from this model are, for SBP, \( h=0.669 \pm 0.015 \) and \( \delta=0.012 \pm 0.002 \) and, for DBP, \( h=0.643 \pm 0.018 \) and \( \delta=0.010 \pm 0.003 \). The estimates of \( h \) correspond to heritabilities, \( h^2 \), of 0.45 and 0.41, respectively.

The estimates of \( \delta \), expressing to what extent the genetic effects are age specific, are not intuitively interpretable. The magnitudes of these age effects are shown in Fig 3 (top and bottom). The expected correlations between relatives, estimated from model 3 as functions of age differences, are drawn as solid lines. The function for the expected correlations, \( r=\exp(-\Delta \delta/2h^2) \), is identical for DZ twins, siblings, and parent-offspring, and the curves smoothly continue independent of kind of relationship. For example, the expected correlation value for SBP in relatives with an age difference of 40 years is 62% of the value for same-aged relatives. This implies that 62% of the genetic variance for SBP at age 20 and at age 60 is attributable to genes that are active at both ages. The remaining genetic variance, 38%, is

### Table 1. Correlations Between Relatives for Age- and Sex-Corrected Blood Pressure

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>No. of Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spouses</td>
<td>.077</td>
<td>.088</td>
<td>23,936</td>
</tr>
<tr>
<td>Father-offspring</td>
<td>.154</td>
<td>.158</td>
<td>19,712</td>
</tr>
<tr>
<td>Mother-offspring</td>
<td>.165</td>
<td>.153</td>
<td>24,039</td>
</tr>
<tr>
<td>Siblings</td>
<td>.204</td>
<td>.191</td>
<td>19,140</td>
</tr>
<tr>
<td>Like-sexed DZ twins</td>
<td>.154</td>
<td>.190</td>
<td>90</td>
</tr>
<tr>
<td>MZ twins</td>
<td>.521</td>
<td>.429</td>
<td>79</td>
</tr>
</tbody>
</table>

DZ indicates dizygotic; and MZ, monozygotic.
caused by genetic effects that are not common to the two ages. For DBP, 67% of the genetic variance at age 20 and at age 60 is explained by common genes, and 33% is explained by age-specific genetic effects.

The figures also show the observed correlations plotted as data points. Not shown are the observed (.521 and .429 for SBP and DBP, respectively) and expected (.423 and .399) correlations for MZ twins.

The model used here assumes invariant heritabilities for blood pressure throughout life. This is a strong assumption because the sum of genetic effects may accumulate or decrease during a lifetime. Such changes would be accompanied by correlations between relatives that vary not only with age differences between relatives but with age itself. To test for such age effects, we classified the data into groups defined by age differences in pairs of relatives and by age. These classifications were done separately for siblings and parents and offspring. Because there are no age differences within twin pairs, twins were classified only by age. Correlations in the various groups are shown in Table 3 for siblings and Table 4 for parents and offspring. The correlations in twins grouped by age are not very informative because of the small numbers and are not presented. The best-fitting model—model 3, specifying $h$ and $\delta$—was fitted simultaneously to all sets of correlation in Tables 3 and 4 together with the age-specific twin correlations. The model constrains the parameters to be equal across age groups. The same model was then refitted to the correlations pooled across age groups. If there is heterogeneity among age groups, the model fit with the age-specific data will be significantly poorer than the model fit with the pooled correlations. There was no clear evidence of heterogeneity for SBP ($\chi^2=34.08, P=.064$), but there was for DBP ($\chi^2=37.29, P=.030$), even though the trend is weak and hardly detectable from inspection of Tables 3 and 4.

A parameter for a linear age effect, that is, a linear change of the expected correlations with mean age of the pair of relatives, was specified for the analyses of the age-specific data. No linear age effect could be detected for SBP. There was a slight tendency for an increase in correlations with age for DBP. The expected correlations in siblings, DZ twins, and parents and offspring increased with the value .0029 with every 10 years of age. The increase in MZ correlation and increase in heritability was double this value. This trend only corresponds to an increase in heritability from .40 at age 20 to .43 at age 80 and is not significant ($\chi^2$ difference between models including and not including the age parameter: $\chi^2=0.86, P=.351$). Thus, the slight age trend that seems to exist for the heritability of DBP is hardly monotonously increasing or decreasing, and probably it is not sufficiently large to violate the assumptions of our model to a noticeable extent.

For the sake of comparison, the parameters $h$, $d$, and $s$ were estimated on the basis of the correlations for the overall sample presented in Table 1 (not including the spouse correlation, which, as in previous models, is assumed to be zero). A model that specifies only $h$ did not fit the data at all ($\chi^2=32.45, P=1.5 \cdot 10^{-6}$ for SBP and $\chi^2=19.39, P=7 \cdot 10^{-4}$ for DBP). Models specifying

| TABLE 3. Correlations Between Siblings by Age and Age Differences |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Age of Oldest Sibling         | 20-29 Years                  | 30-34 Years                  | 35-39 Years                  | 40 Years or More              |
| Age Difference                | SBP  | DBP  | n    | SBP  | DBP  | n    | SBP  | DBP  | n    | SBP  | DBP  | n    |
| 1-3 Years                     | .181 | .126 | 1839 | .218 | .202 | 1642 | .221 | .226 | 1617 | .214 | .226 | 1618 |
| 4-6 Years                     | .178 | .121 | 978  | .190 | .160 | 1450 | .182 | .215 | 1571 | .283 | .225 | 1912 |
| 7 Years or more               | .270 | .187 | 108  | .195 | .178 | 1255 | .239 | .222 | 1935 | .170 | .178 | 3215 |

SBP indicates systolic blood pressure; and DBP, diastolic blood pressure.
in addition to \( h \) fitted the data very well, and substituting \( s \) with \( d \) improved the fit further, although not clearly significantly so, for both SBP and DBP. Estimates from the latter model were \( h^2 = 0.320 \) and \( d^2 = 0.172 \) for SBP and \( h^2 = 0.311 \) and \( d^2 = 0.140 \) for DBP, corresponding to broad heritabilities, \( h^2 + d^2 \), of 0.492 and 0.451, respectively.

For comparison with previous nuclear family studies, the correlation structure for the overall sample was analyzed without the twin data. Removing the twin data left the parameter values almost unchanged: \( h^2 = 0.320 \) and \( d^2 = 0.177 \) for SBP and \( h^2 = 0.311 \) and \( d^2 = 0.142 \) for DBP.

### Discussion

The pattern of familial aggregation of blood pressure in the present and previous studies seems to be one of relatively high MZ twin correlations, intermediate sibling correlations, and low parent-offspring correlations, reflecting age-specific genetic effects rather than genetic dominance or common twin or sibling environment. Heritability estimates from the analyses allowing for age-specific genetic effects are not dramatically different from the broad heritabilities estimated when age differences were not considered. Rather, neglecting age-specific genetic effects resulted in undue substitution of estimated genetic dominance effects for estimated genetic additive effects. The evidence of dominance in the present sample should be judged circumstantial even before the possibility of age-specific effects is introduced, however, and evidence of dominance from previous studies is, at best, scarce. Thus, estimates of dominance may or may not be inflated when age-specific genetic effects are not assessed, and usually the possibility of dominance is wholly disregarded in family studies. In contrast, genetic additive effects are clearly underestimated if age-specific genes are not modeled in studies of relatives with various age differences.

Focusing only on the genetic additive effects or narrow heritability, neglecting age-specific genetic effects probably attenuates the estimates of genetic effects in all types of family studies of blood pressure except for twin studies, the latter left unbiased because cotwins have the same age. But judging from our results, the magnitude of such attenuation is hardly sufficient to bridge the full gap between results from twin studies and other family studies. As with previous nuclear family studies, our overall correlations correspond to heritabilities close to .3 (which are primarily based on the large samples of parents, offspring, and siblings and not on twins). In fact, even the inclusion of data from second-degree relatives (uncles/aunts, nephews/nieces, cousins, and grandparents/grandchildren) gave similar parameter estimates in previous path analyses of correlations from our overall sample. The heritability estimates increased to only 0.41 (SBP) and 0.45 (DBP) after the specification of age-specific genetic effects. Typical heritability values from twin studies are 0.6 to 0.7. In essence, the discrepancy between results from twin studies and other family studies remains partly unresolved.

The finding that the genetic control of SBP and DBP changes continuously with age is of the utmost importance for the understanding of the causality of hypertension. The finding is partly consistent with the recent results of Pérusse et al, who showed an age-specific effect of a single gene. Contrary to the age-specific genetic effects demonstrated in our study, however, this single-gene effect also seemed to be specific for gender. There were no detectable sex differences for the decrease of correlations with age differences in our data, but if moderate, such sex differences could remain undetected even in samples as large as ours. Nonetheless, both studies imply that precise assessment of familial risk for hypertension will ultimately need to reflect these developmental changes in the effects of genes on blood pressure.

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